International Journal of Biomolecules and Biomedicine | IJBB
ISSN: 2221-1063 (Print), 2222-503X (Online)
Website: https://www.innspub.net
Email contact: info@innspub.net
Vol. 21, Issue: 2, p. 1-10, 2025

RESEARCH PAPER OPEN ACCESS

Identification and association of TCF7L2 gene polymorphism with type 2 diabetes risk in north Indian population

Pooja[1], Shubhangi Chaturvedi[1], Shivangi Singh[1], Shefali Singh[2], Dinesh Raj Modi[*1]

[1]Department of Biotechnology, Babasaheb Bhimrao Ambedkar University (A Central University) Vidya Vihar, Raebareli Road, Lucknow-226025, Uttar Pradesh, India

[2]Dr. O.P. Chaudhary Hospital and Research Centre, Raebareli Road, Sector 1, Chaudhary Vihar, Lucknow, Uttar Pradesh, India

Key words: Type 2 diabetes mellitus, TCFL2, Gene variant, Wnt signaling, Haplotype, Prevalence

DOI: https://dx.doi.org/10.12692/ijbb/21.2.1-10 **PUBLISHED: 05 October 2025**

Abstract

Type 2 diabetes Mellitus (T2DM) is a metabolic disorder caused by increased insulin secretion and high blood glucose levels. These increased glucose levels lead to various complications. Here, we investigate the case-control study, where we have selected 200 diabetic and 200 healthy participants from the North Indian population. To understand the function of the rs4506565 & rs11196205 single-nucleotide polymorphism of the TCF7L2 gene in T2DM, I used amplification refractory mutation system (ARMS-PCR) and DNA sequencing. The analysis of the rs4506565 and rs11196205 polymorphisms showed a significant association with T2DM when comparing patients with controls (p-values < 0.05). The TT genotype of rs4506565 shows a higher frequency in the diabetes group (49%) compared to the control group (32.5%), with a model of T/T vs. A/T-A/A: $\chi 2$=12.01, p=0.0008, OR=1.99 and 95% Cl= 1.33-2.99. Similarly, the CC genotype of rs11196205 was more frequent in the diabetes group (51%) compared to the control group (30%), with a model of C/C vs. C/C-G/G: $\chi 2$=18.16, p=0.001, OR=0.41, and 95% Cl=0.27- 0.62 in the North Indian population. Overall, our recent findings suggest that rs4506565 and rs11196205 are positively associated with susceptibility to T2DM.

***Corresponding Author:** Dinesh Raj Modi ✉ drmodilko@gmail.com

INTRODUCTION

Type 2 diabetes mellitus is a group of metabolic disorders due to elevated blood sugar levels that can disrupt insulin secretion. It is characterized by insulin resistance, which leads to poor blood glucose control and hyperglycaemia (Witka *et al.*, 2019). Diabetes mellitus has now been linked to the emergence of the disease. T2DM has shifted from being a common complication of old age to a leading cause of morbidity and mortality among young and middle-aged people (Roden and Shulman, 2019). Nowadays, diabetes affects a significant portion of India's rural and urban areas (Anjana *et al.*, 2023). India, with the world's largest population and a unique genetic makeup, has the second-highest prevalence of T2DM (Rathod *et al.*, 2025). Almost 90% of all diabetes mellitus cases are caused by T2DM (Ma *et al.*, 2022). Although it is a common and treatable condition, it can lead to severe complications such as retinopathy, neuropathy, and various cardiovascular diseases (Movahednasab *et al.*, 2025). Many studies have shown that individuals with a less-dietary-restrictive diet are at a higher risk of causing type 2 diabetes mellitus (T2DM) compared to those who maintain moderate diets and engage in regular exercise. Several signaling pathways are linked and involved in T2DM and other metabolic disorders.

In focuses to our research areas of type 2 diabetes mellitus (T2DM) and related metabolic conditions are linked to components of the Wnt signaling pathway, which plays a crucial role in maintaining normal metabolism (Yu *et al.*, 2024). In this study, we aimed to examine the relationship between key components of the Wnt signaling pathway and T2DM, emphasizing the role of Wnt signaling in the development and progression of T2DM (Ruze *et al.*, 2023). This increased risk is often related to insulin resistance (IR) and β-cell dysfunction (Wu *et al.*, 2014) (Fig. 1). Wingless (Wnt) is a secreted glycoprotein first identified in 1982 by Nusse *et al.* (Willert and Nusse, 2012). Wnt signaling pathway divides into two types i.e., canonical and non-canonical, based on their dependence on TCF/catenin. These pathways activate when Wnt proteins such as Wnt3a, Wnt5a, and Wnt9b bind to their Frizzled (Fzd) receptors. Recent research shows that the Wnt pathway plays a key role in regulating obesity and diabetes (Tian *et al.*, 2024).

The TCF7L2 gene, located about 215.9 kb with 17 exons on chromosome 10q25.3, encodes a transcription factor that plays a vital role in the Wnt signaling pathway (Rajeev and CR, 2019).

This gene influences insulin secretion and glucose production and is expressed in adipose tissue, the liver, and pancreatic islets (Gravand *et al.*, 2018a). The TCF7L2 gene is a key candidate for understanding blood glucose regulation and beta cell function (Mitroi *et al.*, 2022). It contains a high-mobility group box domain, which is essential for cellular development and regulation (del Bosque-Plata *et al.*, 2021). In this study, two high-frequency intronic single-nucleotide polymorphisms (SNPs), rs4506565 and rs11196205, were analysed within the TCF7L2 gene using the Amplification Refractory Mutation System Polymerase Chain Reaction (ARMS-PCR) technique (Verma *et al.*, 2021). The TCF7L2 gene variant rs4506565 has been linked to type 2 diabetes mellitus (T2DM) in Caucasian, East Asian, and South Asian populations (Khan *et al.*, 2021; Peng *et al.*, 2012). This polymorphism involves a point mutation where adenine (A) is replaced by thymine (T) (A>T) at position 112, 996, 282. Minor genetic variations can alter protein activity, potentially affect insulin secretion, and increase the risk of T2DM. The SNP rs4506565 is situated in the intron between exons 5 and 6, likely influencing gene transcription and splicing processes (Badriyya and Achyar, 2020). The gene is also important for proinsulin expression and its processing into insulin. SNP rs11196205 is located in intron 4 and has been associated with T2DM in various regions, including Iceland, Denmark, the USA, and Thailand (Najmiatul *et al.*, 2023). This SNP features a polymorphism at positions 113, 047, 288, where cytosine (C) replaces guanine (G). ARMS-PCR is a method used to detect these types of polymorphisms (Gravand *et al.*, 2018a).

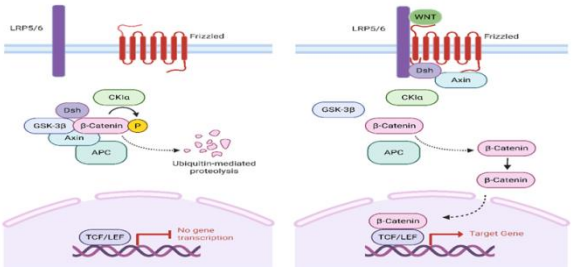

Fig. 1. (A) Diagrammatic representation describes that Wnt initially does not bind to the Axin, GSK, and APC receptor, forming a destruction complex, which leads to the degradation of β-Cat. (B) Wnt binding to the receptor causes the disassembly of the "destruction complex," leading to the release of Axin. Then, β-Cat travels into the nucleus, binds with a transcription factor on DNA, and initiates gene transcription.

MATERIALS AND METHODS

Inclusion and exclusion criteria

We selected male and female participants aged 35–60 years. This review included studies of individuals who were newly diagnosed with T2DM. The measured parameters included BMI, glucose, HbA1c, urea, creatinine, cholesterol, HDL, LDL, and VLDL. Patients with any coexisting conditions, such as type 1 diabetes mellitus, metabolic syndrome, nephropathy, or cardiovascular disease, were excluded.

Study-designed population

The Individuals in this study were selected separately into two groups. The first group included 200 participants who were clinically diagnosed with T2DM, and their ages ranged from 30-60 years. The second group is the healthy control group includes 200 participants. The study samples were collected from O. P. Chaudhary Hospital and Research Centre in Lucknow, Uttar Pradesh, India, between January and May 2025, with fasting glucose levels (≥155 mg/dl) and glycated haemoglobin A1c (HbA1c ≥6.5%). Before sampling, informed consent was given by the study participants. Approval from the ethical committee (The Institutional Ethics Committee of the Sardar Patel Postgraduate Institute of Dental and Medical Sciences, Lucknow, ethically approved the study (registration number EC/NEW/INST/2023/JP/0338) was obtained before the research study, and consent was taken from all participants.

DNA extraction

Genomic DNA was extracted from peripheral blood samples using from phenol-chloroform method (Miller *et al.*, 1988), and the isolated samples were analysed and stored at -20°C for molecular analysis. Agarose gel electrophoresis and UV spectrophotometer were used for qualitative and quantitative DNA analysis, respectively. DNA concentrations varied from 50 to 150 ng/µl, and an A260/A280 ratio between 1.8 and 2.0 was used to verify purity.

Genotyping of rs4506565 and rs11196205 gene polymorphism

Genotype was carried out using the ARMS-PCR using four primers rs4506565 Forward, rs4506565 Reverse, A allele specific rs4506565-F(A), T allele specific rs4506565-R(T) and rs11196205 Forwards, rs11196205 Reverse, C allele specific rs11196205-F(C), G allele specific rs11196205-R(G) in a single PCR, followed by gel electrophoresis. The sequence of four pairs of primers was designed (Table 1). PRIMER1 online software was used to designed a tetra-primer for ARMS-PCR (Dewi *et al.*, 2022). The primers were designed using the TCF7L2 gene sequence (Acc. No. NG_012631) available on the NCBI site. Primer specificity was confirmed using the NCBI BLAST. The PCR conditions by Elsa were used with minor modifications (Elsa Badriyya *et al.*, 2021). PCR (Bio-Rad thermal cycler) was performed in a of 25 µl containing 12.5 µl PCR Master Mix (2X) (GeNei), 0.75 µl of each outer primer, 2 µl of each inner primer (5 pmol of each primer), 2 µl of DNA (50 ng/µl), and 5 µl Mili-Q water. The PCR condition in initial denaturation at 95°C for 3 min, and 95°C for 30 sec, annealing at 63°C for 45 sec, extension at 72°C for 30 sec, and a final extension of 72°C for 5 min for 35 cycles. After amplification, these amplicons were analysed on a 2% agarose gel using electrophoresis Fig. 2A.

Table 1. List of Primer sequence for polymorphisms rs4506565 (A/T) and rs11196205 (C/G)

ARMS-PCR Primer rs4506565 (A>T)	ARMS-PCR Primer rs11196205 (C>G)
(A allele) specific primer	(G allele) specific primer
5'-ATATGGCGACCGAAGTGATA-3'	5'-CAACCATAACTCTCTTACATAGTC-3'
(T allele) specific primer	(C allele) specific primer
5'-CTTGACAAGGGCCCCAA-3'	5'- CTGAAAGTTCTCAACATTTATAACTGCC-3'
Internal Control forward primer	Internal Control forward primer
5'-TACATTCATTAACTCATTTA-3'	5'-TAGATTGTCTCCTTTTGTTTCTGCTAC-3'
Internal Control reverse primer	Internal Control reverse primer
5'-TAAACATCTGACCTTGAAGCCTACC-3'	5'-TAAACATCTGACCTTGAAGCCTACC-3'
A allele amplicon Size 284 bp	G allele amplicon Size 235 bp
T allele amplicon Size 232 bp	C allele amplicon Size 253 bp
Internal control amplicon 500 bp	Internal control amplicon 434 bp

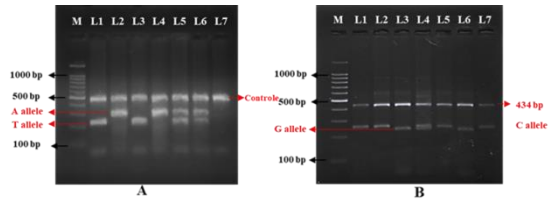

Fig. 2. Analysis on 2% agarose Gel electrophoresis of the ARMS-PCR assay of the TCF7L2 gene
(A). Lane M is a DNA marker, L1& L3 are TT, L2 & L4, AA Genotype, and L5-L6 have the AT genotype, and L7 is the Internal Control with 500 bp. (B). Lane M DNA Marker, L1-L2 & L5, L7 are the CC, L3 & L6 GG Genotype, and L4 has the CG genotype.

PCR condition for rs11196205 in initial denaturation at 95°C for 5 minutes, followed by 30 cycles of 95°C for 30 seconds, annealing at 64°C for 30 seconds, extension at 72°C for 30 seconds, and final extension at 72°C for 5 minutes (Gravand *et al.*, 2018b). After amplification, these resultant products were run on 3% agarose gel electrophoresis, and genotype analysis of rs11196205 was carried out using allele-specific PCR Fig. 2B. There was 99% consistency in the genotyping phenotype observed. Furthermore, a few variants were sent for direct sequencing to confirm the variants.

Statistical analysis

Data analyses were performed by IBM SPSS Statistics 20 (IBM, New York, USA), and descriptive statistics were used to calculate the mean and standard deviation. Allelic and genotype frequencies were calculated using 2×2 and 2×3 contingency tables and the chi-square test. The t-test was used to determine the significance levels of the case and control groups. Based on genetic and phenotype data, significance was examined using ANOVA single-factor analysis. SHESIS software was used for linkage disequilibrium and haplotype analysis. *p*-value of less than 0.05, statistically significant for all tests. The mean ± standard deviation is used to present all data.

RESULTS AND DISCUSSION

Clinical and demographic characteristics of the study

The clinical and demographic information was described in the listed Table 2. In this study, we have used 200 cases and 200 control samples. There is no significant difference between T2DM patients and controls in urea level ($p > 0.05$). However, when compared to controls, T2DM patients had significantly higher BMI, FBG, HbA1c, creatinine, TC, TGL, HDL, and LDL ($p<0.05$).

Association of the TCF7L2 polymorphism with the development of T2DM

There are several methods that have been used for the study of gene polymorphism. The ARMS-PCR method is a very set PCR that is used for the diagnosis of diseases caused by genetic mutations. Designed sets of primers (Inner and outer) were used to amplify allele-specific PCR products from wild-type, heterozygous, and homozygous individuals. In Fig. 2A, detection and amplification of TCF7L2 rs4506565 (A>T) were observed, where the presence of the T allele was indicated by a 500 bp and 232 bp fragment. At the same time, the presence of the (A) allele is determined by with sizes of 500 bp and 284 bp. Analysis of the ARMS-PCR assay for allele (A) and (T), rs4506565 identification. Amplified PCR products were

visualized on agarose 2% of gel electrophoresis. The Lane M is a DNA marker, L1and L3 represent (TT), L2 and L4 (AA) Genotype, and L5-L6 have the (AT) genotype. L7 was Internal Control with 500 bp Fig. 2A. TCF7L2 rs11196205 (C/G), which gives the amplification of product size, in which the 434 bp band is a control, the 253 bp (C) wild type allele, and the 235 bp band for the (G) mutant allele.

Sanger sequencing

DNA was amplified using the respective primer and visualized on a 2% agarose gel to confirm the result. Then, after, 10% of the samples were randomly selected, and products were sequenced at Barcode Biosciences in Bangalore, India. The sequence and the chromatogram obtained after sequencing were aligned to validate the single-nucleotide variations. The confirmed chromatogram results are shown in Fig 3 and 4.

Table 2. Clinical and demographic characteristics of T2DM and control groups

Parameters	T2DM (200)	Control (200)	*p*-value
BMI (kg/m²)	27.17±0.12	22.20±0.14	0.00
FBG (mmol/L)	132.89±0.61	108.16±0.44	0.00
HbA1c (%)	5.59±0.03	3.72±0.02	0.00
Urea (mg %)	29.5±0.35	26.85±2.38	0.27
Creatinine (mg %)	1.40±0.02	0.94±0.01	0.00
TC (mmol/L)	184.17±0.59	135.41±0.40	0.00
TGL (mmol/L)	174.68±1.09	125.13±0.37	0.00
HDL (mmol/L)	29.09±0.35	48.83±0.23	0.00
LDL (mmol/L)	168.26±0.58	137.18±0.48	0.00

Data as mean ± Standard deviation, $p < 0.05$

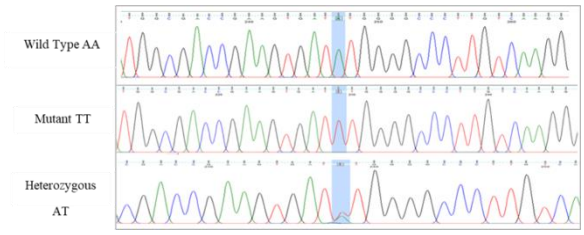

Fig. 3. Sequencing chromatogram showing the homozygous wild-type, heterozygous, and homozygous mutant genotype for A>T TCF7L2 (rs4506565)

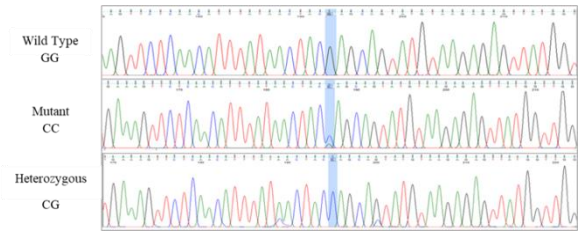

Fig. 4. Sequencing chromatogram showing the homozygous wild-type, heterozygous, and homozygous mutant genotype for C>G TCF7L2 (rs11196205)

Table 3. Genotype and allele frequency of rs4506565 and rs11196205

Polymorphism	Frequencies	Diabetic % N=200	Control % N=200	OR	95% Cl	$\chi 2$	*p*-value
rs4506565	Allele						
	A	147	227				
	T	234	173	2.0887		25.80	0.0001*
	Genotype				Reference		
	AA	64 (32%)	92 (46%)		1.5695 to 2.7797		
	AT	38 (19%)	43 (21.5%)			12.01	.000246*
	TT	98 (49%)	65 (32.5%)				
Genetic models							
Dominant TT vs AT+AA	T/T	98 (49%)	65 (32.5%)	1.9955	1.3303 to 2.9933	11.27	0.0008*
	A/T-A/A	102 (51%)	135 (67.5%)				
Recessive AA vs AT+TT	A/A	64 (32%)	92 (46%)	0.5524	0.3677 to 0.8299	8.23	0.0043
	T/T-A/T	136 (68%)	108 (54%)				
Over-dominant AT vs AA+TT	A/T	38 (19%)	43 (21.5%)	0.8564	0.5225 to 1.3959	0.38	0.5341
	T/T-A/A	162 (81%)	157 (78.5%)				
rs11196205	Allele						
	G	162	234				
	C	238	166	0.4829		25.92	0.0001*
	Genotype				Reference 0.3643		
	GG	64 (32%)	94 (47%)		to 0.6401		

	CG CC	34 (17%) 102 (51%)	46 (23%) 60 (30%)			18.38	00010
Genetic models							
Dominant CC vs CG+GG	C/C C/G-G/G	102 (51%) 98 (49%)	60 (30%) 140 (70%)	0.4418	0.2732 to 0.6206	18.30	0.0001*
Recessive GG vs CG+CC	G/G C/G-C/C	64 (32%) 136 (68%)	94 (47%) 106 (53%)	0.5307	0.3533 to 0.7970	9.41	0.0023
Over-dominant CG vs GG+CC	C/G C/C-G/G	34 (17%) 166 (83%)	46 (23%) 154 (77%)	1.4584	0.8899 to 2.3914	2.25	0.1348

OR – Odds ratio, 95% Cl - 95% confidence interval, * Significant *p*-value

Table 4. Correlation between genotype and phenotype data

Parameters	AA	AT	TT	*p*-value	CC	CG	GG	*p*-value
N%	64 (32%)	38 (19%)	98 (49%)	-	102 (51%)	34 (17%)	64 (32%)	-
BMI	27.28±0.23	27.21±0.29	27.08±0.18	0.78	27.09±0.18	27.20±0.31	27.26±0.22	0.84
FBG	131.82±0.76	133.18±1.31	133.46±1.03	0.49	132.94±0.73	132.47±1.33	133.03±1.36	0.95
HbA1c	5.65±0.07	5.52±0.08	5.58±0.05	0.46	5.55±0.04	5.72±0.11	5.6±0.07	0.27
Urea	30.59±0.71	29.28±0.73	28.86±0.47	0.09	29.45±0.51	29.79±0.86	29.42±0.61	0.93
Creatinine	1.38±0.04	1.50±0.05	1.37±0.03	0.14	1.36±0.03	1.44±0.05	1.43±0.04	0.39
TC	182.39±0.94	186.63±1.47	184.37±0.86	0.04	184.34±1.00	184.32±0.43	183.81±0.95	0.91
TGL	169.53±0.54	179.52±3.31	176.16±1.72	0.002	173.96±1.45	176.47±2.69	174.87±2.09	0.71
HDL	30.35±0.70	28.84±0.69	28.35±0.40	0.04	29.08±0.52	29.29±0.82	28.98±0.60	0.95
LDL	167.18±0.89	168.15±1.40	169.01±0.88	0.38	168.66±0.84	169.29±1.49	167.07±0.94	0.35

Data shown as Mean ± Standard deviation, *p*-value <0.05

Table 5. Haplotype analysis of rs4506565 and rs11196205 control and T2DM groups.

Haplotype	T2DM	Control	$\chi 2$	Person's *p*	Odds ratio 95% CI
A C*	56.03 (0.140)	27.46 (0.069)	10.91	0.000959	2.210 [1.368~3.569]
A G*	109.97(0.275)	198.54 (0.996)	41.38	<.0001	0.385 [0.287~0.516]
T C*	188.97(0.472)	139.54 (0.349)	12.62	0.000384	1.671 [1.258~2.221]
T G*	45.03(0.113)	39.46 (0.086)	1.56	0.211573	1.346 [0.844~2.147]
Global	200	200	44.04	<.0001	

Genotype frequencies of rs4506565 and rs11196205 gene polymorphism among North Indians

The case and control groups enrolled in the study have significantly deviated from HWE at $p<0.05$, as Table 3 shows genotypic data of both rs4506565 and rs11196205 SNPs. In rs4506565, three models were considered, out of which the TT vs AA+AT model showed a significant p-value =0.0008*, and in rs11196205 CC vs GG+CG model showed a significant *p*-value =0.0001*.

Relationship between T2DM susceptibility and genotype and phenotype

We observed that the AT genotype had a higher triglyceride level (179.52±3.31) as compared to the AA (169.53±0.54) and TT (176.16±1.72) genotypes. In rs11196205 (G>C), there is no significant correlation between the genotype and phenotype data of the patients (Table 4).

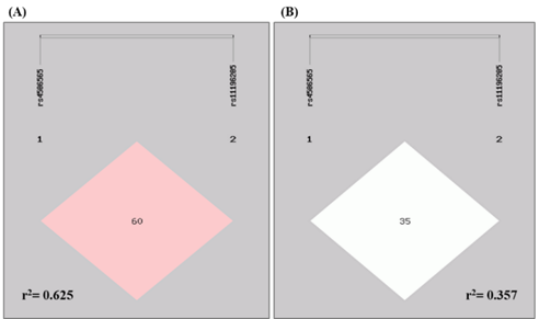

Fig. 5. Linkage disequilibrium analysis of the (r2) of rs4506565 and rs11196205 polymorphism in

Haplotype analysis

Haplotype analysis was performed using these two SNPs: rs4506565 (A>T) and rs11196205 (G>C) (Table 5). Haplotypes T* of rs4506565 and C* of rs11196205

were significantly associated with type 2 diabetes mellitus (p=0.000384). Fig. 5 shows both the SNP's correlation coefficient and Linkage Disequilibrium. SHEsis software was used to analyse the haplotype (Shi and He, 2005).

DISCUSSION

India is currently the second-largest Asian nation after China, with 65.1 million people suffering from Type 2 diabetes mellitus (T2DM). The number of cases is expected to increase upcoming year by 2035 in the number to 109 million (Nanditha *et al.*, 2016). In the Context of India, the North Indian people have a high number of T2DM cases last decades. This is the first information indicating that the North Indian Population links the TCF7L2 polymorphism with T2DM (Chandak *et al.*, 2007). All subsequent research studies conducted on various other populations have replicated the findings of Grant *et al.* (Grant *et al.*, 2006). Hence, we have selected these 2 SNPs for our study. Replication of this association in North Indians who are highly prone to diabetes is of importance (Marzi *et al.*, 2007; Rathod *et al.*, 2025; Wild *et al.*, 2004).

We have studied the cases by taking the sample from O.P. Chaudhary Hospital, Lucknow. We performed the ARMS-PCR by using designed primers to analyse of genetic variation between the cases (Pooja *et al.*, 2025). The study of the relationship between T2DM and TCF7L2 gene polymorphism in North Indians, for the TCF7L2 rs4506565 and rs11196205. To find out whether the rs4506565 and rs11196205 polymorphisms have been associated with type 2 diabetes. Our research demonstrated that data was a statistically significant difference in the allele and frequencies of the rs4506565 and rs11196205 genotypes, polymorphisms between diabetes and healthy individuals. We compared the allele and genotype frequency distribution between patients and healthy controls for both SNPs.

There were significant differences when the genotype frequencies of cases and controls were compared. According to our research, the TCF7L2 gene with polymorphism at rs4506565 (A/T) and rs11196205 (G/C) is highly susceptible to type 2 diabetes in the North Indian Population.

The frequency of the polymorphic genotype (AT, TT) is significantly higher in the patient group (49%) compared to the control group for the polymorphism at rs4506565, and (CG, CC) in the patient group (51%) than in the control group for the polymorphism at rs11196205 in the North Indian Population. Our study found that the T allele of rs450565 is highly associated with type 2 diabetes mellitus, supported by findings in Iraqi Arab patients with the T/T genotype, who were highly susceptible to diabetes those with the A/A genotype (Abdullah and Ali, 2021). Our results suggest the rs11196205 C allele as a possible risk factor that increases the susceptibility of T2D among the North Indian supported by findings in the Iraqi Kurdish population (Agostini *et al.*, 2026).

CONCLUSION

This study concluded that the TT genotype in rs4506565 and the CC genotype in rs11196205 are risk factors for type 2 diabetes mellitus in the North Indian population. Understanding the genetic basis of type 2 diabetes mellitus could inform the development of targeted treatments and interventions. This study will contribute to our understanding of the pathogenesis of debates due to genetic variation and may help regulate clinical phenotype changes through pharmaceutical interventions. The TCF7L2 gene rs4506565 and rs11196205 variants could be used as a genetic marker for T2DM in the North Indian population. Additionally, the polymorphisms in the TCF7L2 gene variant can be used as an indicator of the determinant of individual susceptibility to type 2 diabetes mellitus in North India.

ACKNOWLEDGEMENTS

We hereby express our gratitude to the UGC, New Delhi, India, for the financial support. I am thankful to the laboratory facilities of the Department of Biotechnology, School of Life Sciences, Babasaheb Bhimrao Ambedkar University, Lucknow, Uttar Pradesh, India, and O.P. Chaudhary Hospital OPD,

Lucknow, Uttar Pradesh, India, and the participants of the North India region for their involvement and support in our study.

REFERENCES

Abdullah A, Ali S. 2021. Assessment of the relationship of transcription factor 7-like 2 rs4506565 (T/A) variant with type 2 diabetes in Iraqi Arab patients. Meta Gene **31**.
https://doi.org/10.1016/j.mgene.2021.101008

Agostini LdaC, Coelho LFD, Machado e Silva RB, Silva NN T, Lopes ACF, Belo VA, Coura-Vital W, Teixeira LFdM, Lima AA, da Silva GN. 2026. rs11196205 variant in the TCF7L2 gene is associated with an increased cardiovascular risk in individuals with hypertension and diabetes. Archives of Medical Research **57**, 103268.
https://doi.org/10.1016/j.arcmed.2025.103268

Anjana RM, Unnikrishnan R, Deepa M, Pradeepa R, Tandon N, Das AK, Joshi S, Bajaj S, Jabbar PK, Das HK. 2023. Metabolic non-communicable disease health report of India: The ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). The Lancet Diabetes & Endocrinology **11**, 474–489.
https://doi.org/10.1016/S2213-8587(23)00119-5

Badriyya E, Achyar A, Syamsurizal. 2021. Primer design of SNP rs4506565 transcription factor 7 like 2 (TCF7L2) gene to detect type-2 diabetes mellitus. In: Proceedings of the 2nd International Conference on Contemporary Science and Clinical Pharmacy 2021 (ICCSCP 2021). Atlantis Press. pp. 197–202. https://doi.org/10.2991/ahsr.k.211105.029

Badriyya E, Achyar A. 2020. Primer construction to detect SNP rs11196205 transcription factor 7 like 2 (TCF7L2) using amplification refractory mutation system (ARMS) PCR to detect type-2 diabetes mellitus. Bioscience **4**, 151.
https://doi.org/10.24036/0202042108497-0-00

Chandak GR, Janipalli CS, Bhaskar S, Kulkarni SR, Mohankrishna P, Hattersley AT, Frayling TM, Yajnik CS. 2007. Common variants in the TCF7L2 gene are strongly associated with type 2 diabetes mellitus in the Indian population. Diabetologia **50**, 63–67.
https://doi.org/10.1007/s00125-006-0502-2

Del Bosque-Plata L, Martínez-Martínez E, Espinoza-Camacho MÁ, Gragnoli C. 2021. The role of TCF7L2 in type 2 diabetes. Diabetes **70**, 1220–1228.
https://doi.org/10.2337/db20-0573

Dewi A, Paramita D, Fachiroh J. 2022. Tetra-primer amplification refractory mutation system (ARMS) PCR used to detect 3'UTR rs1948 mutation in CHRNB4. Indonesian Journal of Biotechnology **27**, 1.
https://doi.org/10.22146/ijbiotech.64933

Grant SFA, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir T, Gudmundsdottir T, Gylfason A, Saemundsdottir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K. 2006. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nature Genetics **38**, 320–323.
https://doi.org/10.1038/ng1732

Gravand A, Foroughmand AM, Boroujeni MP. 2018a. A study on the association of TCF7L2 rs11196205 (C/G) and CAPN10 rs3792267 (G/A) polymorphisms with type 2 diabetes mellitus in the southwestern region of Iran. Egyptian Journal of Medical Human Genetics **19**, 403–407.
https://doi.org/10.1016/j.ejmhg.2018.01.007

Gravand A, Foroughmand AM, Boroujeni MP. 2018b. A study on the association of TCF7L2 rs11196205 (C/G) and CAPN10 rs3792267 (G/A) polymorphisms with type 2 diabetes mellitus in the southwestern region of Iran. Egyptian Journal of Medical Human Genetics **19**, 403–407. https://doi.org/10.1016/j.ejmhg.2018.01.007

Khan SM, El Karte N, El Hajj Chehadeh S, Hassoun A, Afandi B, Tay GK, Alsafar H. 2021. Association between type 2 diabetes mellitus and TCF7L2 gene variants in the Emirati population: Genetics of diabetes in the United Arab Emirates. American Journal of Human Biology **33**, e23434. https://doi.org/10.1002/ajhb.23434

Ma CX, Ma XN, Guan CH, Li YD, Mauricio D, Fu SB. 2022. Cardiovascular disease in type 2 diabetes mellitus: Progress toward personalized management. Cardiovascular Diabetology **21**, 74. https://doi.org/10.1186/s12933-022-01516-6

Marzi C, Huth C, Kolz M, Grallert H, Meisinger C, Wichmann HE, Rathmann W, Herder C, Illig T. 2007. Variants of the transcription factor 7-like 2 gene (TCF7L2) are strongly associated with type 2 diabetes but not with the metabolic syndrome in the MONICA/KORA surveys. Hormone and Metabolic Research **39**, 46–52. https://doi.org/10.1055/s-2007-957345

Miller SA, Dykes DD, Polesky HF. 1988. A simple salting-out procedure for extracting DNA from human nucleated cells. Nucleic Acids Research **16**, 1215–1215. https://doi.org/10.1093/nar/16.3.1215

Mitroi AF, Leopa N, Dumitru E, Brînzan C, Tocia C, Dumitru A, Popescu RC. 2022. Association of TCF7L2, CASC8 and GREM1 polymorphisms in patients with colorectal cancer and type II diabetes mellitus. Genes **13**. https://doi.org/10.3390/genes13081297

Movahednasab M, Dianat-Moghadam H, Khodadad S, Nedaeinia R, Safabakhsh S, Ferns G, Salehi R. 2025. GLP-1-based therapies for type 2 diabetes: From single, dual and triple agonists to endogenous GLP-1 production and L-cell differentiation. Diabetology & Metabolic Syndrome **17**, 60. https://doi.org/10.1186/s13098-025-01623-w

Najmiatul F, Zuhanna FN, Yosmar R. 2023. The relationship of diuretic therapy and clinical outcome on quality of life of patients with congestive heart failure. Malaysian Journal of Public Health Medicine **23**, 99–103. https://www.mjphm.org/index.php/mjphm/article/view/1981

Nanditha A, Ma RC, Ramachandran A, Snehalatha C, Chan JC, Chia KS, Shaw JE, Zimmet PZ. 2016. Diabetes in Asia and the Pacific: Implications for the global epidemic. Diabetes Care **39**, 472–485. https://doi.org/10.2337/dc15-1536

Peng S, Zhu Y, Lü B, Xu F, Li X, Lai M. 2012. TCF7L2 gene polymorphisms and type 2 diabetes risk: A comprehensive and updated meta-analysis involving 121,174 subjects. Mutagenesis **28**, 25–37. https://doi.org/10.1093/mutage/ges048

Pooja S, Shivangi C, Singh S, Raj Modi D. 2025. Interrelation of TCF7L2 gene polymorphism with type 2 diabetes patients of North Indian population. Biochemical and Cellular Archives **25**. https://doi.org/10.51470/bca.2025.25.1.000

Rajeev G, CR WDS. 2019. Role of Wnt signaling pathway in type 2 diabetes mellitus: An overview. RGUHS Journal of Medical Sciences **9**. https://doi.org/10.26463/rjms.9_4_6

Rathod L, Khan S, Mishra S, Das D, Bora K, Shubham S, Singh S, Kumar M, Tiwari RR, Tiwari A. 2025. Genetic variants and type 2 diabetes in India: A systematic review and meta-analysis of associated polymorphisms in case-control studies. The Lancet Regional Health–Southeast Asia **32**. https://doi.org/10.1016/j.lansea.2024.100518

Roden M, Shulman GI. 2019. The integrative biology of type 2 diabetes. Nature **576**, 51–60. https://doi.org/10.1038/s41586-019-1797-8

Ruze R, Song J, Yin X, Chen Y, Xu R, Wang C, Zhao Y. 2023. Mechanisms of obesity- and diabetes mellitus-related pancreatic carcinogenesis: A comprehensive and systematic review. Signal Transduction and Targeted Therapy **8**, 139. https://doi.org/10.1038/s41392-023-01376-w

Shi Y, He L. 2005. SHEsis: A powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell Research **15**, 97–98. https://doi.org/10.1038/sj.cr.7290272

Tian S, Zhao H, Song H. 2024. Shared signaling pathways and targeted therapy by natural bioactive compounds for obesity and type 2 diabetes. Critical Reviews in Food Science and Nutrition **64**, 5039–5056. https://doi.org/10.1080/10408398.2022.2148090

Verma S, Srivastava N, Banerjee M. 2021. Genetic polymorphisms in TCF7L2 and PPARG genes and susceptibility to type 2 diabetes mellitus. Meta Gene **28**, 100864. https://doi.org/10.1016/j.mgene.2021.100864

Wild S, Roglic G, Green A, Sicree R, King H. 2004. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care **27**, 1047–1053. https://doi.org/10.2337/diacare.27.5.1047

Willert K, Nusse R. 2012. Wnt proteins. Cold Spring Harbor Perspectives in Biology **4**, a007864.

Witka BZ, Oktaviani DJ, Marcellino M, Barliana MI, Abdulah R. 2019. Type 2 diabetes-associated genetic polymorphisms as potential disease predictors. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy **12**, 2689–2706. https://doi.org/10.2337/diacare.27.5.1047

Wu Y, Ding Y, Tanaka Y, Zhang W. 2014. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. International Journal of Medical Sciences **11**, 1185. https://doi.org/10.7150/ijms.10001

Yu M, Qin K, Fan J, Zhao G, Zhao P, Zeng W, Chen C, Wang A, Wang Y, Zhong J, Zhu Y, Wagstaff W, Haydon RC, Luu HH, Ho SC, Lee MJ, Strelzow J, Reid RR, He TC. 2024. The evolving roles of Wnt signaling in stem cell proliferation and differentiation, the development of human diseases, and therapeutic opportunities. Genes & Diseases **11**, 101026. https://doi.org/10.1016/j.gendis.2023.04.042